EXHIBIT 6j

Bertoldi 2020: Exposure to APAP in both the 1st and 2nd trimester of pregnancy was associated with lower WRAVMA drawing scores (β −1.51, 95% CI −2.92, −0.10) in Project Viva.

Bornehag 2018: The adjusted odds ratio (OR) for LD among girls whose mothers reported >6 vs. 0 APAP tablets was 5.92 (95% confidence interval (CI) 1.10–31.94). The OR for LD in girls whose mothers' urinary APAP was in the highest compared to the lowest quartile was 10.34 (95% CI 1.37–77.86).

Brandlistuen 2013: Children exposed to prenatal APAP for more than 28 days had poorer gross motor development (β 0.24), communication (β 0.20), externalizing behavior (β 0.28), internalizing behavior (β 0.14), and higher activity levels (β 0.24) compared with unexposed children.

Golding 2019: Adjusted finding identified 12 independent associations with APAP use at $P < .05$, four of which were at $P < .0001$ (all related to child behaviors reported by the mother at 42 and 47 months, e.g., conduct problems: adjusted mean score +0.22 (95% confidence interval 0.10-0.33).

Laue 2019: The effect of in utero APAP exposure on the Coding subtest was marginally significantly different among boys and girls, with girls performing significantly better on the task with higher levels of acetaminophen compared with girls with undetectable levels of exposure (βgirls, low = 2.83 [0.97, 4.70], βgirls, high = 1.95 [-0.03, 3.93], βboys, low = .02 [-1.78, 1.81], βboys, high = -.39 [-2.09, 1.31], pinteraction = .06).

Liew 2016a: Children born to mothers using acetaminophen without reporting fever scored on average 3.4 points lower on performance IQ compared with offspring of mothers who neither experienced fever nor took acetaminophen (mean difference = -3.1, 95% CI -5.7 to -0.45).

Parker 2019: Acetaminophen use during pregnancy was associated with increased total behavior problem scores and a higher risk of clinical behavior problems according to mother reports (mean difference = 2.2 points; 95% CI ,0.3-4.1 and risk ratio = 1.93, 95% CI ,0.99-3.76).

Rifas-Shiman 2019: Higher prenatal acetaminophen and any ibuprofen were associated with higher parent-rated BRIEF global scores (β = 1.64 points; 95% CI ,0.59-2.68 and β = 1.56 points; ,95% CI ,0.19-2.92).

Stergiakouli 2016: Maternal prenatal acetaminophen use at 18 and 32 weeks of pregnancy was associated with increased odds of conduct problems, hyperactivity symptoms, emotional symptoms, and total difficulties in offspring (risk ratio = 1.42, ,95% CI ,1.25-1.62; risk ratio = ,1.,31; ,95% CI ,1.,16-1.,49; risk ratio = ,1.,29; ,95% CI ,1.,09-1.,53; and risk ratio = ,1.,46; ,95% CI ,1.,21-1.,77 respectively)

Tovo-Rodrigues 2020: This study did not find any association between prenatal acetaminophen exposure and neurodevelopmental performance at 24 months or emotional and behavioral problems at 48 months in Brazilian children.

Tronnes 2019: This study found that exposure to acetaminophen in three trimesters increased the risk of internalizing behavior problems (RR 1.36, 95% CI 1.02-1.80) and borderline externalizing behavior

problems (RR 1.22, 95% CI 0.93-1.60) in preschool-aged children from the Norwegian Mother and Child Cohort Study.

Vlenterie 2016: This study found that long-term paracetamol exposure during pregnancy was associated with communication problems (OR 1.38, 95% CI 0.98-1.95) and delayed motor milestone attainment (OR 1.35, 95% CI 1.07-1.70) among children at 18 months of age from the Danish National Birth Cohort.

D. Summary of AOP and APAP Causation of Neurodevelopmental Disorders (Meta-Analysis)

There are several meta-analyses that have been performed on the available epidemiological studies. These studies draw upon the above studies and meta-analysis and also report increased risks for ASD and ADHD with perinatal exposures to APAP.

Alemany 2021
This meta-analysis aimed to assess the association between maternal use of acetaminophen during pregnancy and the risk of attention deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) in offspring.[448] The study included 6 European cohort studies with a total of 73,881 mother-child pairs.

The results showed that maternal use of acetaminophen during pregnancy was associated with an increased risk of ADHD in offspring (pooled relative risk [RR] = 1.29, 95% confidence interval [CI] = 1.20–1.39). The association was stronger for male offspring (RR = 1.35, 95% CI = 1.23–1.48) than for female offspring (RR = 1.18, 95% CI = 1.06–1.32). Maternal use of acetaminophen during pregnancy was also associated with an increased risk of ASD in offspring (pooled RR = 1.21, 95% CI = 1.08–1.36).

The conclusion of the meta-analysis is that maternal use of acetaminophen during pregnancy is associated with an increased risk of ADHD and ASD in offspring.

Gou 2019
This study examined association between maternal APAP use during pregnancy and the risk of ADHD in offspring via meta-analysis.[449] Eight cohort studies with a total of 244,940 participants were included for this analysis.

Maternal exposure to APAP during pregnancy increased the risk of ADHD in offspring with a pooled adjusted risk ratio of 1.25 (95% confidence interval = 1.17-1.34). Children exposed prenatally to acetaminophen in the third trimester seemed to have the greatest risk of developing ADHD (risk ratio: 1.26; 95% confidence interval = 1.08-1.47). In addition, a longer duration of maternal acetaminophen use during pregnancy was correlated with a higher risk ratio.

This study supports that increased use of APAP during pregnancy is associated with a higher risk of ADHD development in children due to fetal exposure. Children whose mothers used acetaminophen for

[448] Alemany et al. Prenatal and postnatal exposure to acetaminophen in relation to autism spectrum and attention-deficit and hyperactivity symptoms in childhood: Meta-analysis in six European population-based cohorts. Eur J Epidemiol. 2021 Oct;36(10):993-1004. doi: 10.1007/s10654-021-00754-4. Epub 2021 May 28. PMID: 34046850; PMCID: PMC8542535.
[449] Gou et al. Association of maternal prenatal acetaminophen use with the risk of attention deficit/hyperactivity disorder in offspring: A meta-analysis. Aust N Z J Psychiatry. 2019 Mar;53(3):195-206. doi: 10.1177/0004867418823276. Epub 2019 Jan 17. PMID: 30654621.

28 or more days during gestation had a higher risk of developing ADHD (risk ratio: 1.63; 95% confidence interval = 1.23-2.16). One limitation noted was that these findings are based on three studies (Liew et al., 2014; Stergiakouli et al., 2016; Ystrom et al., 2017).

The study also reported that the risk of ADHD was higher when APAP was used during the third trimester compared to the first and second trimesters. This could be related to the rapid growth and structural changes happening in the fetal brain during that time.

Gender differences were also explored, and some studies suggested stronger effects in girls. The prevalence of ADHD is generally higher in boys than in girls, but the reasons for this difference are not fully understood and may involve biological factors and susceptibility to early-life stressors. The study reports conflicting findings on gender differences in ADHD, calling for further research to better understand the relationship.

The meta-analysis concludes that there is an association between maternal APAP use during pregnancy and an increased risk of ADHD in offspring. The timing and duration of APAP use during pregnancy has a major effect on the risk of ADHD.

Kim 2019

This study is an umbrella review of meta-analyses that examined the associations between environmental risk factors, biomarkers, and autism spectrum disorder.[450] The authors used various statistical tests to assess the strength and validity of the evidence for each association. The eligible meta-analyses were classified into five levels of evidence based on a series of statistical tests and criteria. The levels of evidence were: convincing (class I), highly suggestive (class II), suggestive (class III), weak (class IV), and not significant. The criteria included the p value, the number of cases, the heterogeneity, the small study effects, the excess significance bias, the credibility ceiling, and the prediction interval. The authors also did sensitivity analyses to check the robustness of the associations. They found that only seven environmental risk factors, mostly related to maternal age, metabolic syndrome, and antidepressant use, had convincing evidence of association with autism spectrum disorder.

The authors reported that APAP use during pregnancy was one of the environmental risk factors that was graded as highly suggestive evidence (class II) of association with autism spectrum disorder. The random effects summary estimate for this association was a relative risk of 1.20 (95% CI 1.14–1.26) based on five cohort studies with more than 1000 cases of autism spectrum disorder. However, this association showed signs of small study effects and was not significant under 10% credibility ceiling, meaning that it could be affected by bias or confounding factors.

Kim 2020

The article is an umbrella review of meta-analyses that examines the association between potential environmental risk factors, environmental protective factors, or peripheral biomarkers with ADHD. [451] The eligible meta-analyses were classified according to the strength of the evidence of potential environmental risk factors, environmental protective factors, and peripheral biomarkers for ADHD into

[450] Kim et al. Environmental risk factors and biomarkers for autism spectrum disorder: an umbrella review of the evidence. Lancet Psychiatry. 2019 Jul;6(7):590-600. doi: 10.1016/S2215-0366(19)30181-6. PMID: 31230684.

[451] Kim et al. Environmental risk factors, protective factors, and peripheral biomarkers for ADHD: an umbrella review. Lancet Psychiatry. 2020 Nov;7(11):955-970. doi: 10.1016/S2215-0366(20)30312-6. PMID: 33069318.

five classes: convincing (class I), highly suggestive (class II), suggestive (class III), weak (class IV), and not significant (NS). Criteria for each level of evidence were p values under a random effects model, the number of ADHD cases, the statistical significance of the largest study, the I^2 statistic, small study effects, excess significance bias, random effects summary estimate under a 10% credibility ceiling, and the 95% prediction interval.

The study found that maternal pre-pregnancy obesity, childhood eczema, hypertensive disorders during pregnancy, pre-eclampsia, and maternal APAP exposure during pregnancy were strongly associated with ADHD. Maternal APAP exposure during pregnancy was found to have a "convincing" association with ADHD. The study found that evidence of association was convincing (class I) for maternal APAP exposure during pregnancy (RR 1.25, 95% CI 1.17 to 1.34). The authors note that there is a possibility of residual confounding, as not all potential confounders were adjusted for in the included studies.

Patel 2022

The article is a systematic review of the long-term safety of prenatal and neonatal exposure to paracetamol, a common antipyretic and analgesic drug.[452] The authors searched three electronic databases for original research studies that examined the occurrence of neurodevelopmental, atopic or reproductive adverse outcomes in children exposed to APAP in the womb or within the first four weeks of life.They included 30 studies in the final review, most of which were observational epidemiologic and cohort studies. The majority of the studies focused on prenatal exposure, while only three studies reported on neonatal exposure.

The authors found that prenatal APAP exposure was associated with an increased risk of neurodevelopmental, atopic and reproductive adverse outcomes in children, such as asthma, wheezing, eczema, behavior problems, attention deficit hyperactivity disorder (ADHD), autism spectrum disorder (ASD), reduced anogenital distance (AGD) and delayed pubertal development. They also found that neonatal paracetamol exposure was possibly correlated with long-term adverse outcomes in one study.

The authors suggest caution in the use of APAP during pregnancy and early life.

Ricci 2023

This systematic review and meta-analysis reviewed 22 studies including 23 cohorts with a total of 367,775 participants that aimed to summarize the literature on the association between in utero acetaminophen exposure and child neurodevelopmental outcomes and assess the extent to which the association is due to confounding by indication.[453]

The authors searched OVID for Medline, Embase, and PsycINFO, and EBSCO for CINAHL, from inception to August 18, 2022. The authors included all peer-reviewed, English-language studies on in utero APAP exposure and child neurodevelopmental outcomes. Data were extracted using a standardized form created a priori. The quality of the studies was assessed using the Systematic Assessment of Quality in Observational Research. The authors generated pooled risk ratios (RR) for outcomes examined by ≥3

[452] Patel et al. Long-Term Safety of Prenatal and Neonatal Exposure to Paracetamol: A Systematic Review. Int J Environ Res Public Health. 2022 Feb 14;19(4):2128. doi: 10.3390/ijerph19042128. PMID: 35206317; PMCID: PMC8871754.
[453] Ricci et al. In utero acetaminophen exposure and child neurodevelopmental outcomes: Systematic review and meta-analysis. Paediatr Perinat Epidemiol. 2023 Mar 20. doi: 10.1111/ppe.12963. Epub ahead of print. PMID: 36939050.

studies using random-effects models; outcomes that could not be meta-analyzed were narratively summarized following Synthesis Without Meta-Analysis guidelines.

The quality assessments resulted in 13.6% of studies being classified as high, 59.1% as medium, 22.7% as low, and 4.5% as very low quality. The study found that *in utero* APAP exposure was associated with an elevated risk of ADHD (unadjusted pooled risk ratio 1.32, 95% confidence interval (1.20-1.44); I^2 = 47%, n = 7 studies), and the association remained after adjusting for confounders, including indications for APAP use (adjusted pooled risk ratio 1.34, 95% confidence interval (1.15-1.55); I^2 = 50%, n = 4 studies). The I^2 statistic is used to assess the degree of heterogeneity or variability across studies included in the analysis. The reported 47-50% would be considered moderate heterogeneity. It indicates that there is some heterogeneity between studies beyond what can be attributed to chance alone.

In conclusion, this systematic review and meta-analysis reported a significant association between in utero APAP exposure and development of ADHD that was not explained by confounding by indication.

Masarwa 2018

This meta-analysis aimed to assess the role of potential unmeasured confounding in the estimation of the association between acetaminophen use during pregnancy and the risk of attention deficit hyperactivity disorder (ADHD) in offspring.[454] The study included seven observational studies that examined this association. The results showed that when adjusted estimates were pooled across all studies, the risk ratio (RR) for ADHD was 1.35 (95% confidence interval [CI] 1.25, 1.46; I2 = 48%). Sensitivity analysis for unmeasured confounding showed that a confounder of 1.69 on the RR scale would reduce to 10% the proportion of studies with a true effect size of RR >1.10.

The conclusion of the meta-analysis is that bias analysis suggests that the previously reported association between acetaminophen use during pregnancy and an increased risk of ADHD in offspring may be due to unmeasured confounding, and that our ability to conclude a causal association is limited.

Masarwa 2020

This study aimed to assess the role of potential unmeasured confounding in the estimation of the association between acetaminophen use during pregnancy and the risk of attention deficit hyperactivity ADHD in offspring, through bias analysis.[455] Bias analysis involves identifying and assessing the potential sources of bias in a study and evaluating their potential impact on the study results. The goal is to understand how biases may have influenced the observed associations and to estimate the direction and magnitude of the bias. The secondary objective was to assess the roles of selection bias and exposure misclassification.

The study conducted a systematic review and meta-analysis of observational studies examining the association between acetaminophen use during pregnancy and the risk of ADHD in offspring. The authors searched PubMed, Embase, and Web of Science for relevant studies published up to December 2019. The authors included cohort and case-control studies that reported on the association between APAP use

[454] Masarwa et al. Prenatal Exposure to Acetaminophen and Risk for Attention Deficit Hyperactivity Disorder and Autistic Spectrum Disorder: A Systematic Review, Meta-Analysis, and Meta-Regression Analysis of Cohort Studies. Am J Epidemiol. 2018 Aug 1;187(8):1817-1827. doi: 10.1093/aje/kwy086. PMID: 29688261.

[455] Masarwa et al. Acetaminophen use during pregnancy and the risk of attention deficit hyperactivity disorder: A causal association or bias? Paediatr Perinat Epidemiol. 2020 May;34(3):309-317. doi: 10.1111/ppe.12615. Epub 2020 Jan 9. PMID: 31916282.

during pregnancy and the risk of ADHD in offspring. Studies were excluded if they did not report on APAP exposure during pregnancy or if they did not report on ADHD as an outcome. Two reviewers independently extracted data from the included studies, including study characteristics, exposure and outcome definitions, and results. Discrepancies were resolved through discussion. The authors assessed the quality of the included studies using the Newcastle-Ottawa Scale for cohort and case-control studies.

The authors conducted a random-effects meta-analysis to pool adjusted risk estimates across studies. They also conducted a bias analysis to assess the potential impact of unmeasured confounding, selection bias, and exposure misclassification on the results. The meta-analysis included seven studies with a total of 132,738 mother-child pairs. When adjusted estimates were pooled across all studies, the risk ratio (RR) for ADHD was 1.35 (95% confidence interval (CI), 1.25-1.46; $I^2 = 48\%$). However, bias analysis suggests that the previously reported association between APAP use during pregnancy and an increased risk of ADHD in offspring may be due to unmeasured confounding.

The study concludes that their ability to conclude a causal association between APAP use during pregnancy and an increased risk of ADHD in offspring is limited due to potential unmeasured confounding. Unmeasured confounding occurs when a variable that is associated with both the exposure and the outcome is not measured or controlled for in the study.

Weight of the Evidence for Meta-Analyses Investigating the Association Between APAP and ASD and ADHD.

Weight of evidence analysis is a systematic approach to evaluating the strength of scientific evidence by considering the quality, quantity, and consistency of the available data. A meta-analysis is a statistical analysis that combines the results of multiple scientific studies to produce a single estimate of the effect of an intervention or exposure. Using the hierarchy of evidence approach, meta-analyses are reported to provide level 1 evidence, see Figure 1, as they synthesize the results of multiple studies on a specific topic. However, not all meta-analyses are equally reliable, and they may vary in their methods, quality, and conclusions. Therefore, it is important to critically appraise the meta-analyses and assess their strengths and limitations. Here is a summary of the findings and odds ratios reported by each meta-analysis in the current web page context, followed by a conclusion based on the evidence:

Alemany 2021: This meta-analysis found that maternal use of APAP during pregnancy was associated with an increased risk of ADHD (pooled relative risk [RR] = 1.29, 95% confidence interval [CI] = 1.20–1.39) and ASD (pooled RR = 1.21, 95% CI = 1.08–1.36) in offspring. The association was stronger for male offspring than for female offspring. The meta-analysis included 6 European Cohort studies with a total of 73,881mother-child pairs.

Gou 2019: This meta-analysis found that maternal use of APAP during pregnancy increased the risk of ADHD in offspring with a pooled adjusted risk ratio of 1.25 (95% CI = 1.17-1.34). The risk was higher for children exposed to APAP in the third trimester and for longer duration of use. The meta-analysis included eight studies with a total of 244,940 participants.

Kim 2019: This umbrella review of meta-analyses found that APAP use during pregnancy was one of the environmental risk factors that had highly suggestive evidence (class II) of association with ASD. The random effects summary estimate for this association was a relative risk of 1.20 (95% CI 1.14–1.26) based

on five cohort studies with more than 1000 cases of ASD. However, this association showed signs of small study effects and was not significant under 10% credibility ceiling, meaning that it could be affected by bias or confounding factors.

Kim 2020: This umbrella review of meta-analyses found that APAP use during pregnancy had convincing evidence (class I) of association with ADHD. The random effects summary estimate for this association was a relative risk of 1.25 (95% CI 1.17 to 1.34) based on seven studies with a total of 132,738 mother-child pairs. However, the authors noted that there was a possibility of residual confounding, as not all potential confounders were adjusted for in the included studies.

Patel 2022: This systematic review found that prenatal APAP exposure was associated with an increased risk of neurodevelopmental, atopic and reproductive adverse outcomes in children, such as asthma, wheezing, eczema, behavior problems, ADHD, ASD, reduced anogenital distance and delayed pubertal development. The review included 30 studies, most of which were observational epidemiologic and cohort studies.

Ricci 2023: This systematic review and meta-analysis found that in utero APAP exposure was associated with an elevated risk of ADHD (unadjusted pooled RR 1.32, 95% CI 1.20-1.44; $I^2 = 47\%$, n = 7 studies), and the association remained after adjusting for confounders, including indications for APAP use (adjusted pooled RR 1.34, 95% CI 1.15-1.55; $I^2 = 50\%$, n = 4 studies). The meta-analysis included 22 studies with a total of 367,775 participants.

Masarwa 2018: This meta-analysis found that when adjusted estimates were pooled across all studies, the RR for ADHD was 1.35 (95% CI 1.25, 1.46; I2 = 48%). However, bias analysis suggested that the previously reported association between APAP use during pregnancy and an increased risk of ADHD in offspring may be due to unmeasured confounding, and that the ability to conclude a causal association is limited. The meta-analysis included seven studies with a total of 132,738 mother-child pairs.

Masarwa 2020: This study conducted a bias analysis to assess the potential impact of unmeasured confounding, selection bias, and exposure misclassification on the results of the previous meta-analysis by Masarwa et al., 2018. The study confirmed that the observed association between APAP use during pregnancy and an increased risk of ADHD in offspring may be due to unmeasured confounding.

Based on the hierarchy of evidence approach, most of the meta-analyses provide high-quality evidence that maternal use of APAP during pregnancy is associated with an increased risk of NDDs, including ADHD and ASD, in offspring.

Overall, the weight of evidence indicates **APAP has "clear evidence" of developmental toxicity**, based on the consistent finding in multiple meta-analyses. **There are moderate associations between maternal use of APAP during pregnancy and an increased risk of ADHD and ASD in offspring.** These reviewed meta-analyses consistently confirmed and reported associations between APAP and ASD and ADHD, including dose-response by dose or duration.

E. Other Relevant Reviews of the Literature on APAP and Brain Development

Bauer 2021

This review and consensus statement summarizes the evidence on prenatal exposure to APAP (also referenced as paracetamol/acetaminophen) altering fetal development and increasing the risks of certain neurodevelopmental, reproductive, and urogenital disorders. They call for precautionary action through focused research efforts and by increasing awareness among health professionals and pregnant women.

The authors recommend that pregnant women should be cautioned at the beginning of pregnancy to forego APAP unless its use is medically indicated; consult with a physician or pharmacist if they are uncertain whether use is indicated and before using on a long-term basis; and minimize exposure by using the lowest effective dose for the shortest possible time. They suggest specific actions to implement these recommendations.

This consensus statement reflects the concerns of the authors and was signed by 91 scientists, clinicians, and public health professionals from across the globe. The authors acknowledge that APAP is an important medication and alternatives for treatment of high fever and severe pain are limited. However, they believe that taking a precautionary approach is warranted given the growing body of experimental and epidemiological research suggesting potential risks associated with prenatal exposure to APAP.

Buhrer 2021

This article discusses the growing concerns that APAP use during pregnancy may cause attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) in the offspring. It reports a growing number of epidemiological studies suggest that relative risks for these disorders increase by an average of about 25% following intrauterine paracetamol exposure. The data analyzed point to a dose-effect relationship but cannot fully account for unmeasured confounders, notably indication and genetic transmission.

The study also summarizes the altered behavior reported in offspring of paracetamol-treated pregnant rats, and paracetamol given at or prior to day 10 (PND10) in newborn mice resulted in altered locomotor activity in response to a novel home environment in adulthood and blunted the analgesic effect of paracetamol given to adult animals.

The study concludes that given the widespread use of paracetamol during pregnancy and the lack of safe alternatives, its impact on the developing brain deserves further investigation. Caution is warranted when considering long-term use of paracetamol during pregnancy; however, women with severe pain conditions should not be deprived of appropriate treatments.

Cendejas-Hernandez 2022

This study is a systematic review that aimed to assess the safety of APAP use in infants and children for neurodevelopment.[456] The authors searched PubMed, Embase, and Web of Science for relevant studies published up to December 2019. The authors included studies that reported on the association between APAP use in infants and children and neurodevelopmental outcomes. The authors extracted data from the included studies, including study characteristics, exposure and outcome definitions, and results. The

[456] Cendejas-Hernandez et al. Paracetamol (acetaminophen) use in infants and children was never shown to be safe for neurodevelopment: a systematic review with citation tracking. Eur J Pediatr. 2022 May;181(5):1835-1857. doi: 10.1007/s00431-022-04407-w. Epub 2022 Feb 17. PMID: 35175416; PMCID: PMC9056471.

authors conducted a systematic review with citation tracking to assess the evidence on the safety of APAP use in infants and children for neurodevelopment.

The study concludes that although widely believed by pediatricians and parents to be safe for use in infants and children when used as directed, increasing evidence indicates that early life exposure to APAP may cause long-term neurodevelopmental problems.

Havdahl 2022
The study used data from the Norwegian Mother, Father and Child Cohort Study (MoBa) to assess parental genetic liability to attention-deficit/hyperactivity disorder (ADHD), autism, and schizophrenia.

Outcome definition and determination: The outcomes examined were offspring neurodevelopmental conditions, including ADHD, autism, and schizophrenia.

Control group: The control group would be offspring without neurodevelopmental conditions.

Study size: The study included data from the MoBa cohort, which recruited pregnant women in Norway between 1999 and 2008.

Confounding factors or biases and how or if they were controlled: The study adjusted for a number of factors, including maternal age, education, smoking, alcohol use, pre-pregnancy body mass index (BMI), parity, marital status, household income, life events during pregnancy, symptoms of depression/anxiety during pregnancy, use of other pain medication during pregnancy, fever/infection during pregnancy, child sex, gestational age at birth, birth weight, and breastfeeding duration.

Overall, the study reported that genetic liability to neurodevelopmental conditions that is passed from mothers to children was associated with several pregnancy-related factors and may therefore confound associations between these pregnancy-related factors and offspring neurodevelopment that have previously been thought to be causal. The study concluded that further research is needed to clarify these associations.

F. Prenatal APAP Exposure and Other Outcomes

In this section, I review studies investigating prenatal exposure to APAP and birth outcomes other than impaired learning, cognitive, or social behavior.

Gervin 2017
This is a cohort study design using samples selected from the Norwegian Mother and Child Cohort (MoBa).[457]

[457] Gervin et al. Long-term prenatal exposure to paracetamol is associated with DNA methylation differences in children diagnosed with ADHD. Clin Epigenetics. 2017 Aug 2;9:77. doi: 10.1186/s13148-017-0376-9. PMID: 28785368; PMCID: PMC5540511.

Information used to determine exposure: Information about paracetamol use was based on three questionnaires completed during pregnancy. Long-term use was defined as use of paracetamol for 20 days or more during pregnancy.

Outcome definition and determination: The outcome of interest was DNA methylation differences associated with prenatal exposure to paracetamol and ADHD in cord blood samples. ADHD diagnoses were obtained from the Norwegian Patient Registry (NPR) from 2008 to 2014.

Control group: The control group consisted of 96 samples that were unexposed to paracetamol and without ADHD.

Study size: The study included a total of 384 samples, with 96 samples in each of the four categories: unexposed to paracetamol without ADHD, exposed to paracetamol without ADHD, unexposed to paracetamol with ADHD, and exposed to paracetamol with ADHD.

Confounding factors or biases and how or if they were controlled: Potential covariates such as infant sex, gestational age at delivery, maternal age, smoking, and alcohol consumption during pregnancy were included in the statistical model. The study also corrected for cord blood cell-type composition between groups using a suitable cord blood reference data set.

Results: The study reported that prenatal exposure to paracetamol/acetaminophen and its precursor aniline impaired masculinization of the male brain and behavior.

The study concludes that their findings support that prenatal exposure to APAP and its precursor aniline impairs masculinization of the male brain and behavior, and that in susceptible individuals, prenatal long-term exposure to APAP is associated with DNA methylation in genes involved in oxidative stress.

Eslamimehr 2022

This study is a cohort study that examined the association between prenatal APAP use and acetaminophen metabolites with DNA methylation of newborns.[458]

Exposure: The exposure of interest in this study was prenatal APAP use and APAP metabolites. Information on prenatal acetaminophen use was obtained from maternal self-reported questionnaires. This is a study limitation, because self-reported maternal APAP use during pregnancy may be subject to recall bias or measurement error. Acetaminophen metabolites were also measured in maternal urine samples collected during pregnancy, which mitigates this limitation.

Outcome definition and determination: The outcome of interest in this study was DNA methylation of newborns. DNA methylation was measured in cord blood samples collected at birth. DNA, cytosine-phosphate-guanine (CpG) CpG, dinucleotides were examined. CpG islands refer to a specific DNA sequence region that contains a high frequency of CpG dinucleotides. CpG islands are characterized by having a high density of CpG sites, which are usually methylated. Methylation refers to the addition of a

[458] Eslamimehr et al. Association of prenatal acetaminophen use and acetaminophen metabolites with DNA methylation of newborns: analysis of two consecutive generations of the Isle of Wight birth cohort. Environ Epigenet. 2022 Feb 2;8(1):dvac002. doi: 10.1093/eep/dvac002. PMID: 35317219; PMCID: PMC8933617.

methyl group (CH3) to the cytosine nucleotide of a CpG dinucleotide. Methylation of CpG islands in gene promoters is associated with gene silencing or reduced gene expression. In general, the presence of a CpG island near a gene promoter region is associated with active transcription and gene expression, while methylation of CpG sites within the island can lead to gene repression.

Control group: This study did not have a traditional control group as it was a cohort study following pregnancies among women who did not report using acetaminophen during pregnancy.

Study size: The study included 1,056 mother-child pairs from two consecutive generations of the Isle of Wight Birth Cohort.

Confounding factors or biases and how or if they were controlled: The study adjusted for several potential confounding factors, including maternal age, pre-pregnancy body mass index (BMI), smoking status, alcohol consumption, parity, education level, and child sex. Additionally, the study used propensity score matching to control for potential confounding by indication.

Results: The study found that 21 differential DNA methylation sites in cord blood were associated with reported maternal acetaminophen intake in the F2 generation. For 11 of these CpG sites, an indication bias was excluded and five were replicated in F2 with metabolite clusters. In addition, metabolite clusters showed associations with 25 CpGs in the F0-F1 discovery analysis, of which five CpGs were replicated in the F2-generation.

The study concludes that these findings support that prenatal APAP use has an impact on the epigenetic profile of newborns. This is important because DNA methylation is a mechanism by which environmental exposures can influence gene expression and potentially impact health outcomes later in life.

Arneja 2020

The study is a prospective pregnancy and birth cohort study.[459]

Information used to determine exposure: Use of over-the-counter (OTC) analgesics, including acetaminophen, was identified from questionnaires. Exposure was categorized by timing of use: (i) prepregnancy: in the 3 months before pregnancy, (ii) early pregnancy: in the first 12–16 weeks of pregnancy, and (iii) mid–late pregnancy: between completion of the first questionnaire and 28–32 weeks of gestation. Acetaminophen use was also categorized by frequency into: never, less than once per week, and one or more times per week.

Outcome definition and determination: The outcomes examined were preterm birth, low birthweight, and small for gestational age. Information on the baby's sex, birthweight, and gestational age was derived from clinical data collected from hospital medical charts.

Control group: The control group would be women who never used acetaminophen.

Study size: The study included 1,200 women within the Ontario Birth Study who delivered between January 2013 and June 2017.

[459] Arneja et al. Association between maternal acetaminophen use and adverse birth outcomes in a pregnancy and birth cohort. Pediatr Res. 2020 Jun;87(7):1263-1269. doi: 10.1038/s41390-019-0726-8. Epub 2019 Dec 18. PMID: 31852009.

Confounding factors or biases and how or if they were controlled: Covariates included a priori defined variables based on literature review and hypothesized relationships between acetaminophen use and birth outcomes. Information on covariates was obtained from lifestyle questionnaires. Multivariable adjusted models included age, smoking in the 3 months before pregnancy, body mass index (BMI) at baseline, maternal ethnicity, education, fever during pregnancy, paternal smoking in the 3 months before pregnancy, a comorbidity index created as a sum of the number of pre-existing conditions reported by each individual, and participants' use of other pain medications including OTC nonsteroidal anti-inflammatory drugs and prescription pain medications such as diclofenac, morphine, oxycodone, and codeine during the respective time periods.

Results: the study found that children born to mothers who used acetaminophen in the 3 months before pregnancy had a higher risk of having low birthweight and being born small for gestational age. Further, results presented evidence of dose response with more frequent use of acetaminophen being associated with increased risk of the offspring being born small for gestational age. During pregnancy, however, maternal use of APAP was not associated with the examined adverse birth outcomes: preterm birth, low birthweight, and small for gestational age. In addition, continuous use of acetaminophen (relative to never use) was not associated with any of the examined birth outcomes.

The study concluded that pre-pregnancy APAP use is associated with higher risk of adverse birth outcomes.

Baker 2022

This was a prospective cohort study.[460]

Information used to determine exposure: APAP exposure was determined by measuring APAP levels in meconium samples collected at birth.

Outcome definition and determination: The outcomes of interest were birthweight, gestational age, preterm birth, size for gestational age, gestational diabetes, preeclampsia, and high blood pressure. These outcomes were determined using medical records and standardized definitions.

Control group: The control group consisted of infants with no detectable levels of APAP in their meconium samples.

Study size: The study included 1,062 mother-infant pairs.

Confounding factors or biases and how or if they were controlled: The study controlled for potential confounding factors such as maternal age, pre-pregnancy BMI, smoking status, alcohol consumption, and socioeconomic status using multivariable regression models.

[460] Baker et al. Association of Prenatal Acetaminophen Exposure Measured in Meconium With Adverse Birth Outcomes in a Canadian Birth Cohort. Front Pediatr. 2022 Apr 5;10:828089. doi: 10.3389/fped.2022.828089. PMID: 35450103; PMCID: PMC9017809.

Limitations: (1) The homogeneity of the GESTE cohort limits the generalizability of results despite minimizing confounding. Variations in the association of meconium APAP with birthweight were observed between individuals recruited during pregnancy and at delivery, possibly due to different distributions of unmeasured genetic and environmental modifiers in each group. (2) The study had a small sample size of nearly 400 mother-child pairs, resulting in few events for certain outcomes such as early prematurity and severe preeclampsia. (3) The exclusion of extremely preterm deliveries may introduce selection bias and limit conclusions about preterm birth. (4) The study lacked information to control for indications of APAP use during pregnancy, potentially leading to confounding by indication. (5) The detection of APAP in meconium may be influenced by the size of infants, but inverse causality is unlikely. (6) Self-reported APAP use and correlating it with meconium levels were not conducted, limiting knowledge of dosage and timing of exposure. (7) Meconium may have limited utility for studying severe prematurity and early pregnancy outcomes since it forms in later stages of pregnancy. (8) The long-term storage of meconium samples at −80°C raises the possibility of sample degradation, although the stability of APAP in meconium under these conditions is unknown.

Results: The results indicated that prenatal acetaminophen exposure was linked to a 136 g decrease in birthweight, a 20% higher weekly delivery hazard, and a more than 60% reduced likelihood of being born large for gestational age. No associations were found between prenatal APAP use and small for gestational age, preterm birth, or any pregnancy complications.

Vedel 2022

The study was a qualitative study based on a short questionnaire.[461]

Information used to determine exposure: The study used self-reported data from pregnant women who completed a questionnaire regarding their use of APAP during pregnancy. This is a study limitation, because self-reported maternal APAP use during pregnancy may be subject to recall bias or measurement error.

Outcome definition and determination: The outcome of the study was to investigate the feasibility of executing a randomized clinical trial (RCT) in light of the results of a new qualitative study on APAP use during pregnancy.

Control group: Not applicable as this was a qualitative study.

Study size: A total of 232 pregnant women completed the questionnaire with a mean gestational age of 13 weeks and 6 days.

Confounding factors or biases and how or if they were controlled: Not applicable as this was a qualitative study.

Results: The study reported that 48% of the women had taken APAP after recognizing their pregnancy, and only 6% had taken APAP weekly or more than weekly. Overall, 34% would participate in an RCT regarding APAP and 49% would not. The rest were in doubt. Of the women who had taken APAP after

[461] Vedel et al. The use of paracetamol during pregnancy: A qualitative study and possible strategies for a clinical trial. PLoS One. 2022 Sep 13;17(9):e0271537. doi: 10.1371/journal.pone.0271537. PMID: 36099269; PMCID: PMC9469947.

becoming pregnant, 44% would not participate in an RCT. That leaves a total of 27% who had taken any APAP in the first trimester of pregnancy that would potentially participate in an RCT.

G. Conclusions Based on WoE of Epidemiological Studies

As reviewed above, the developing brain is vulnerability to oxidative damage and neurotoxicity during the Brain Growth Spurt (BGS). In humans, the BGS peaks at around birth but continues during early post-natal development. As a result, the vulnerability of the fetal brain during the third-trimester to the toxic effects of APAP is also present in the infant brain in the weeks after birth. As a result, infant exposure to APAP can also cause ASD and ADHD. In an epidemiological study limited to APAP exposure during pregnancy, any ASD or ADHD caused by infant exposure to APAP postnatally could be a significant factor that would lower the reported odds ratio for *in utero* associations between APAP and ASD and ADHD. This misclassification was raised as a concern in several studies, as self-reporting was the primary mode of determining APAP exposures. Studies that measured APAP do not support such misclassification or confounding by indication. For example, the study from Ji et al. 2020 that relied on measurements of APAP in cord plasma reported that children in the second tertile (OR = 2.14; CI 0.93-5.13) and third tertile (OR = 3.62; CI 1.62-8.60) had a higher odds of an ASD diagnosis compared to studies that relied on maternal self-reporting. This suggests that studies based on maternal self-reporting are biased towards the null, and that the actual risks of ASD are higher than reported in such studies.

In addition, certain factors identified as potential confounders that are controlled for in a study can be mediators or modifiers of toxicity. For example, a sibling control study would mask the effects of a genetic vulnerability (e.g., a deficiency in glutathione synthesis or transport) that is present in siblings. Such a genetic vulnerability may not cause ASD or ADHD without additional environmental stress. In such a case, genetic or nutritional modifiers are not an alternative causal path, they are within the same oxidative stress AOP. Regarding familial and sibling interactions, Dr. Baccarelli's report includes a cogent explanation of how a sibling-control study would mask or mitigate the association between APAP and ASD or ADHD.

Independent review of the available epidemiological evidence indicates "some evidence" for APAP exposure causing ADHD or ASD. The majority of these studies are limited because of self-reporting. The conclusions based on available meta-analyses are that maternal use of APAP during pregnancy provides "clear evidence" of increased risk of ADHD and ASD in offspring. These data consistently show associations between APAP and ASD and ADHD, including dose-response by dose or duration. Two meta-analyses, both by the same group/first author, do present "unmeasured confounding" as an alternative explanation. Three studies analyzed exposure via biological fluids, including cord blood and meconium. Of the three studies analyzing biological fluids, two of the three demonstrated a dose-responsive increase in ADHD or ASD risk with higher levels of APAP exposure. Collectively, these studies provide "clear evidence" for APAP exposure causing ADHD and ASD.

I have also reviewed the Expert Report of Dr. Andrea Baccarelli that addresses the epidemiological evidence, and I concur with his analysis and conclusions.

Based on the hierarchy of evidence approach, most of the meta-analyses provide high-quality evidence that maternal use of APAP during pregnancy is associated with an increased risk of NDDs, including ADHD and ASD, in offspring.

Overall, the weight of evidence indicates **APAP has "clear evidence" of developmental toxicity**, based on the consistent finding on increased risk of ASD and ADHD in multiple meta-analyses. **There are**

moderate associations between maternal use of APAP during pregnancy and an increased risk of ADHD and ASD in offspring. These reviewed meta-analyses consistently confirmed and reported associations between APAP and ASD and ADHD, including dose-response by dose or duration.

AUTISM GENETICS & EPIGENETICS

A key concept in teratology is that the majority of structural birth defects are caused by the combined effects of individual host susceptibility (genetic factors) that interact with exogenous exposures (environmental factors) in other words, gene-environmental interactions. Such interactions or effect modification can arise between a given gene or collection of genes, and various environmental factors. The complexity of such interactions can quickly become challenging to elucidate analytically and to test experimentally in a rigorous hypothesis-driven manner. Does the genetic factor exacerbate the environmental factor (or vice versa) to increase overall risk for the observed birth defect? Alternatively, are both the genetic factor and the environmental factor necessary to increase the defect risk? Additional questions can also arise as to whose genetic background (mother, father, or infant) and whose exposure (mother or father) is most pertinent. As with other observational studies of human disorders, identification of risks between a gene and an environmental factor requires a careful assessment of whether the observed relationship has arisen by chance or is the result of some bias. For example, has some selective force in the study design or methods allowed an excess of cases (or a deficiency of controls) with both the genetic and the environmental factor(s)?

Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder with a multifactorial etiology, that includes genetic and environmental factors. ASD affects nearly 2% of children in the United States, and both genetic and environmental factors are proposed to be involved in the etiology. No single gene has been identified as the cause of ASD, but genetics are considered a factor in the etiology of autism with hundreds of genes being implicated in its pathogenesis.

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder that is reported to affect 3-6% of school-age children and shows evidence of familial inheritance. ADHD is characterized by symptoms of inattention, hyperactivity, and impulsivity. Like ASD, ADHD is a complex disorder that is influenced by both genetic and environmental factors. While no single gene has been identified as the sole cause of ADHD, several genes have been associated with the disorder.

Genetic studies report that ASD and ADHD are not solely the result of genetic factors and that the rise in the prevalence of the diseases cannot be explained by genetics alone. Studies also demonstrate that APAP targets a large number of genes identified as making someone susceptible to ASD.

Carter and Blizard examined environmental pollutants including pesticides, heavy metals, bisphenol A, phthalates and many others in food, cosmetics or household products for potential roles of environmental pollutants in the etiology of Autism Spectrum Disorder (ASD).[462] The study analyzed gene/environment interactions in autism using 206 autism susceptibility genes (ASGs) from the Autworks database to interrogate ~1 million chemical/gene interactions in the comparative toxicogenomics database. The study found that a number of compounds identified in epidemiology selectively target autism genes, including

[462] Carter and Blizard. Autism genes are selectively targeted by environmental pollutants including pesticides, heavy metals, bisphenol A, phthalates and many others in food, cosmetics or household products. Neurochem Int. 2016 Oct 27:S0197-0186(16)30197-8. doi: 10.1016/j.neuint.2016.10.011. Epub ahead of print. PMID: 27984170.

APAP. The study authors found that the number of autism susceptibility genes targeted by APAP (9,176) exceeded all other tested compounds, except for Valproic Acid (VPA), a compound that is used to induce and model ASD symptoms in rodents.

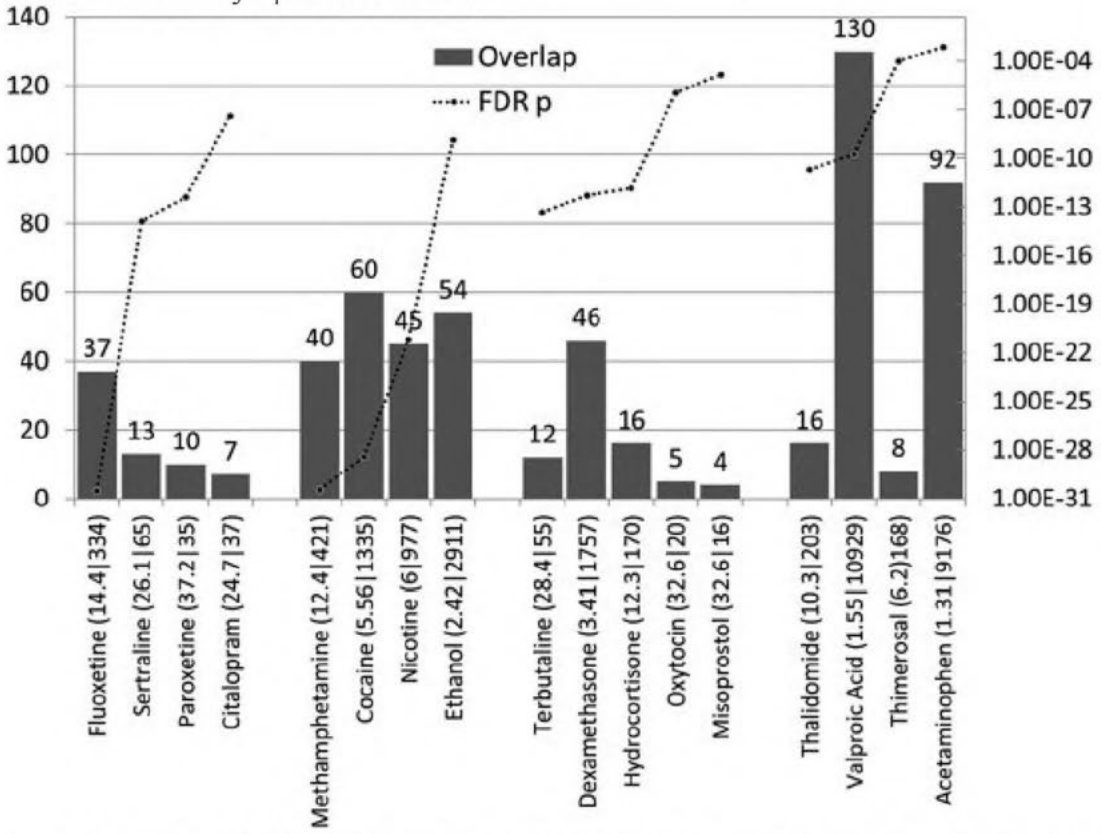

Figure 33. The Number of Autism Susceptibility Genes (ASGs). Reported ASGs are affected by diverse endocrine disruptors. (Number of ASGs = left axis, p values = right axis). The enrichment ratio and the total number of genes affected by each compound are shown after each compound name. Acetaminophen is shown in the last bar, with significant enrichment of ASGs.

Santos et al. discusses the potential role of gene-environment interactions in the etiology of ASD.[463] The study aimed to identify genes involved in the regulation of xenobiotic detoxification or the function of physiological barriers (the XenoReg genes) presenting predicted damaging variants in subjects with ASD and to understand their interaction patterns with ubiquitous xenobiotics previously implicated in this disorder. The study defined a panel of 519 XenoReg genes through literature review and database queries and inspected large ASD datasets for predicted damaging Single Nucleotide Variants (SNVs) or Copy Number Variants (CNVs) in XenoReg genes. The interrogation of ASD datasets for variants in the XenoReg gene panel identified 77 genes with high evidence for a role in ASD, according to pre-specified prioritization criteria. These include 47 genes encoding detoxification enzymes and 30 genes encoding proteins involved in physiological barrier function, among which 15 are previous reported candidates for ASD. The study concludes that individuals carrying predicted damaging variants in high evidence XenoReg genes are likely to have less efficient detoxification systems or impaired physiological barriers and can therefore be particularly susceptible to early life exposure to ubiquitous xenobiotics, which elicit

[463] Santos et al. A Role for Gene-Environment Interactions in Autism Spectrum Disorder Is Supported by Variants in Genes Regulating the Effects of Exposure to Xenobiotics. Front Neurosci. 2022 May 19;16:862315. doi: 10.3389/fnins.2022.862315. PMID: 35663546; PMCID: PMC9161282.

neuropathological mechanisms in the immature brain. As exposure to environmental factors may be mitigated for individuals with risk variants, this work provides new perspectives to personalized prevention and health management policies for ASD.

There is no single gene implicated in the etiology of ADHD, but various gene mutations have been associated with ADHD, including:

DRD4: This gene encodes the dopamine receptor D4, which is involved in the regulation of attention, motivation, and reward. Variations in this gene have been associated with an increased risk of ADHD.[464, 465]

DAT1 / SLC6A3: This gene encodes the dopamine transporter, which is involved in the regulation of dopamine levels in the brain. Variations in this gene have been associated with an increased risk of ADHD.[466, 467, 468]

Epigenetics

Epigenetics concerns itself with the manner in which environmental factors, working through chemical signals or proteins modify the expression of genes without changing the structure of DNA (deoxyribonucleic acid). The nucleic acid chain that makes up the genes in the cell's nucleus is DNA. The messenger molecule that carries information from the nucleus out to the cytoplasm of the cell is RNA (ribonucleic acid). The capacity of various environmental toxicants to disrupt the function of these nucleic acids, or to destroy them outright, has an important bearing on causation and mechanism.

It is now well established that environmental exposures during the first 1000 days post-conception can result in epigenetic imprints that are transmissible to the baby and beyond to subsequent generations. Some of the environmental risk factors which shape the genetic and epigenetic signature of the offspring include: maternal nutritional status and stress, xenobiotics, recreational exposures (alcohol, drugs and smoking) as well as maternal occupational contaminants.[469,470] Early life is a critical period during which the differentiation process leading to specialized cells from the pluripotent cells, is mediated by 'epigenetic remodeling' such that genes that do not have to be expressed in a particular tissue type are turned off, while maintaining active gene expression for genes in those tissues for which it is appropriate to remain

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[464] LaHoste Get al. Dopamine D4 receptor gene polymorphism is associated with attention deficit hyperactivity disorder. Mol Psychiatry. 1996 May;1(2):121-4. PMID: 9118321.

[465] Grady et al. High prevalence of rare dopamine receptor D4 alleles in children diagnosed with attention-deficit hyperactivity disorder. Mol Psychiatry. 2003 May;8(5):536-45. doi: 10.1038/sj.mp.4001350. PMID: 12808433.

[466] Cook et al. Association of attention-deficit disorder and the dopamine transporter gene. Am J Hum Genet. 1995 Apr;56(4):993-8. PMID: 7717410; PMCID: PMC1801209.

[467] Gill et al. Confirmation of association between attention deficit hyperactivity disorder and a dopamine transporter polymorphism. Mol Psychiatry. 1997 Jul;2(4):311-3. doi: 10.1038/sj.mp.4000290. PMID: 9246671.

[468] Daly et al. Mapping susceptibility loci in attention deficit hyperactivity disorder: preferential transmission of parental alleles at DAT1, DBH and DRD5 to affected children. Mol Psychiatry. 1999 Mar;4(2):192-6. doi: 10.1038/sj.mp.4000510. PMID: 10208453.

[469] Hanson and Gluckman. Early developmental conditioning of later health and disease: physiology or pathophysiology? Physiol Rev. 2014 Oct;94(4):1027-76. doi: 10.1152/physrev.00029.2013. PMID: 25287859; PMCID: PMC4187033.

[470] Burton and Metcalfe. Can environmental conditions experienced in early life influence future generations? Proc Biol Sci. 2014 May 7;281(1785):20140311. doi: 10.1098/rspb.2014.0311. PMID: 24807254; PMCID: PMC4024293.

active.[471,472] In this context, epigenetic alterations via DNA methylation and post-translational modifications work to differentiate cells properly. DNA methylation depends on the activity of specific enzymes called DNA methyltransferases (DNMTs), which promotes the methylation (the addition of CH_3 groups) to specific DNA nucleotides within a region of a gene referred to as CpG islands, at the promoter of a gene leading to a progressive switching off of the gene. Anything that inhibits the interaction between chemical signaling proteins called transcription factors and the promoter region of a gene due to the presence of methyl groups (CH_3) limits their binding with RNA-polymerases that are required to turn on gene expression.[473] At the same time, methylation of regulatory regions within any given gene, serves as an additional control of gene expression.

As the term implies, epigenetics represents a level of genetic regulation that is not limited to the messages coded in the DNA sequence. Genomic mutational catalogs are now available for numerous cancers, producing databases such as COSMIC: the Catalogue Of Somatic Mutations In Cancer.[474] Analysis of this data has produced novel mutational signatures associated with chemical exposures, such as smoking.[475] Epigenetic fingerprints are also emerging and are associated with specific chemical exposures.[476] In both genetics and epigenetics, signatures emerge because some regions of the genome are more susceptible to specific chemicals than others, producing genetic and epigenetic/epigenomic alterations characteristic of environmental factors. There has been progress in analytical tools and interpretation of genomic architecture, but our understanding of genomics and epigenomics is by no means complete. While telomere-to-telomere genomics is filling in genomic gaps and becoming more available,[477] there is still more information needed before the epigenetic regulation of all protein coding genes is properly interrogated and understood.[478]

LaSalle reviewed epigenetic signatures for ASD.[479] The review discusses how epigenetic investigations, including DNA methylation, have emerged as a novel way to capture the complex interface of multivariate autism spectrum disorder (ASD) etiologies. Epigenome-wide association studies using human brain and surrogate accessible tissues have revealed some convergent genes that are epigenetically altered in ASD, many of which overlap with known genetic risk factors. Epigenomic signatures defined by DNA methylation from surrogate tissues such as placenta and cord blood can reflect past differences in fetal

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[471] de Rooij et al. Prenatal Undernutrition and Autonomic Function in Adulthood. Psychosom Med. 2016 Nov/Dec;78(9):991-997. doi: 10.1097/PSY.0000000000000393. PMID: 27606796; PMCID: PMC5097462.

[472] Dominguez-Salas et al. Maternal nutritional status, C(1) metabolism and offspring DNA methylation: a review of current evidence in human subjects. Proc Nutr Soc. 2012 Feb;71(1):154-65. doi: 10.1017/S0029665111003338. Epub 2011 Nov 29. PMID: 22124338; PMCID: PMC3491641.

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[474] Tate et al. COSMIC: the Catalogue Of Somatic Mutations In Cancer. Nucleic Acids Res. 2019 Jan 8;47(D1):D941-D947. doi: 10.1093/nar/gky1015. PMID: 30371878; PMCID: PMC6323903.

[475] Islam and Alexandrov LB. Bioinformatic Methods to Identify Mutational Signatures in Cancer. Methods Mol Biol. 2021;2185:447-473. doi: 10.1007/978-1-0716-0810-4_28. PMID: 33165866.

[476] Jeremias et al. Prospects for incorporation of epigenetic biomarkers in human health and environmental risk assessment of chemicals. Biol Rev Camb Philos Soc. 2020 Jun;95(3):822-846. doi: 10.1111/brv.12589. Epub 2020 Feb 11. PMID: 32045110.

[477] Nurk et al. The complete sequence of a human genome. Science. 2022 Apr;376(6588):44-53. doi: 10.1126/science.abj6987. Epub 2022 Mar 31. PMID: 35357919; PMCID: PMC9186530.

[478] Gershman et al. Epigenetic patterns in a complete human genome. Science. 2022 Apr;376(6588):eabj5089. doi: 10.1126/science.abj5089. Epub 2022 Apr 1. PMID: 35357915; PMCID: PMC9170183.

[479] LaSalle JM. Epigenomic signatures reveal mechanistic clues and predictive markers for autism spectrum disorder. Mol Psychiatry. 2023 Jan 17. doi: 10.1038/s41380-022-01917-9. Epub ahead of print. PMID: 36650278.